Rejection under 35 U.S.C. §102

Claims 1, 6-9, 11-15 and 47 are rejected under 35 U.S.C. §102 as anticipated by Southern U.S. Patent 5,667,667. The Examiner contends that Southern teaches a "method for electrochemical placement of a material at a specific location on a **porous** substrate." (emphasis added) Specifically, the Examiner cites Southern column 4, line 39 and column 1 lines 47-54 to attribute a "porous" substrate to Southern. Applicant respectfully disagrees and traverses this rejection because Southern is mischaracterized as disclosing a "porous" substrate.

Southern provides an array having alternating cathode and anode rows, an electrolyte solution and an overlaying glass surface that is anything but "porous." The passage cited by the Examiner (column 4 line 39) provides "on the surface of a glass plate." Applicant asserts that a glass plate is not a porous substrate. Moreover, the claimed invention would not function with a glass plate. The entire nature of the term "porous" is that it denotes permeability to fluids, and consequently, oligomers are synthesized within a porous structure and not solely on its surface. The nature of a glass plate is that it is not permeable to fluids and consequently oligomer synthesis occurs only on its surface. Therefore, Southern does not teach the importance of a porous substrate. Accordingly, claims 1,6-9,11-15 and 47 are not anticipated becausethey all include the element "on a porous substrate" which is not taught by Southern. .

Rejection under 35 U.S.C. §103

Claims 1-9 and 11-51 were rejected under 35 U.S.C. §103 as unpatentable over Heller et al. (U.S. Patent 5,929,208) in view of Southern (as described above). The Examiner acknowledges the fundamental difference between Heller and the claimed invention ("The difference between the Heller method and that of Applicants is that Heller employs an electrophoretic technique while Applicant teaches an electrochemical method of combinatorial synthesis."). That is not just a mere "difference" it is a conceptual quantum leap. The Examiner further alleges that this alleged "difference" or now "deficiency" is disclosed by Southern. Specifically, Southern provides an electrochemical process for synthesizing on a surface "adjacent" (not proximate) to the electrode having a solution of electrolyte interposed between the electrode and the surface (glass surface) where the oligonucleotide is synthesized *in situ*. Applicant respectfully traverses this rejection because there is no suggestion to combine an electrophoresis process to move fully formed oligonucleotides of Heller with an electrochemistry process for *in situ* synthesis of Southern.

In order to combine two or more references there must be some expressed suggestion found in the references and not gleaned from the present invention. There is no suggestion found in either Southern or Heller to suggest their combination. In the field of microarrays or biochips involving oligonucleotides, there are two fundamentally different approaches to synthesize such

microarrays. They are either (1) *in situ* synthesis, that is building an oligonucleotide base-by-base; or (2) locating fully formed oligonucleotides to specific sites by electric field or charge (*e.g.*, Heller) or by physical spotting (many references). The present invention provides an *in situ* synthesis technique involving electrochemistry and certain distinctive elements, such as (1) a porous substrate forming a three dimensional matrix by virtue of its porosity; and (2) certain buffers, such as described in claims 2-5, that limit pH shifts and prevent "cross-talk" between adjacent regions of porous substrate "proximate" to their respective electrodes.

Heller, by contrast teaches a procedure that creates an electric field to attract fully formed oligonucleotides to locations. The method of Heller (like Hollis et al. U.S. Patent 5,653,030 that appears to be a duplicate of Heller) is not in situ synthesis but rather a form of spotting that uses electric fields in a solution to attract oppositely charged molecules. Heller does not use electrochemically-generated reagents and does not use a buffer solution. The Examiner has alleged (with reference to claims 2, 18, 43 and 48 on page 6 of the Office Action) that Heller "disclosed placing of a buffer solution in contact with the electrode at the surface of the substrate to prevent electrochemically generated reagents from leaving the locality of the electrode." The Examiner cites column 22 lines 25-37 for this alleged teaching in Heller. The Examiner has misapplied Heller. No such teaching is found in Heller because Heller does not use or desire to have electrochemically-generated reagents present. Indeed, such reagents interfere with the desired electric field Heller is attempting to create.

The Examiner alleges that Heller discloses a phosphate buffer. Applicant respectfully disagrees with the Examiner's characterization of Heller and asserts that the context in which Heller teaches the use of a phosphate buffer (See Example 2, cited by the Examiner) in fact teaches away from the present invention. As stated in the cited paragraph (Heller column 22, lines 47-48) "Unbound DNA is repulsed while the covalently attached DNA remains." This disclosure does not teach the use of electrochemically-generated reagents for *in situ* synthesis of the present invention. Instead, this example (used by the Examiner out-of-context) refers to electrophoresis of charged DNA that is the thrust of Heller. An obviating reference must be used only in the context of the entire teachings of that reference and cannot be used selectively for a buffer here or there. . Here, the fact that a buffer is used in Heller's electrophoretic process (as it is used in allbiological electrophoresis experiments) is irrelevant because, as stated above, this process clearly teaches away from the *in situ* synthesis process of the claimed invention.

The Examiner rejects claims 2, 18, 43 and 48 based on alleged teachings by Heller. Applicant respectfully disagrees and traverses asserting that the Examiner has misconstrued the passages cited within the context of Heller. Specifically, , the Heller passage cited by the Examiner refers to capillaries to transport liquids and prevent bubbles and does not, in any way,

disclose or suggest what the Examiner states ("placing of a buffer solution in contact with the electrode at the surface of the substrate to prevent electrochemically generated reagents from leaving the locality of the electrode.") The cited passage is unrelated to the Examiner's characterization which, appears to be quoted from the claimed invention and is nowhere disclosed or suggested in Heller (or Southern).

The Examiner rejects claims 3-5, 19-21 and 49-51 based on Heller's disclosure of a phosphate buffer in the electrophoretic process.. Applicant respectfully traverses, citing our arguments above regarding Heller's teaching of buffers. Furthemore Applicant reassert the above arguments regarding the patentability of the independent claims over Heller in view of Southern from which claims 3-5, 19-21 and 49-51 depend.

With regard to claim 6, the Examiner alleges discloses "preformed molecules having protected chemical functional groups at non-bonding sites." Applicant respectfully traverses and asserts that the Examiner has mischaracterized the citation fromHeller. The passage referenced in the Office Action (Heller column 15, lines 48-58) refers to reversing polarity of the electrophoresis field and there is no reference to protected chemical function groups ("Any unreacted binding entity is removed by reversing the polarity of that specific micro-location, and **electrophoresing** it to a disposal location." Emphasis added). Therefore, Heller was mis-applied as related to claim 6.

With regard to claims 7 and 22, the Examiner alleges that Heller discloses amino acids in column 21 line 30 and in column 6 lines 24-41. Applicant respectfully disagrees and traverses by asserting that he Examiner has mischaracterized the cited reference. Specifically, Heller disclosesan animo moiety not an amino acid in column 21, line 30. In the string of every biological chemical ever used at column 6 lines 24-41 cited by the Examiner, Heller is referring to "a biological or synthetic molecule that has specific binding affinity to another molecule, through covalent bonding or non-covalent bonding." Essentially this is a superficial review of organic chemistry. Applicant admits that amino acids are known molecules and described in most basic organic chemistry textbooks and biochemistry text books. No further teaching is provided in Heller.

The Examiner rejected claims 8, 37 and 44 for the proposition that Heller "employ[s] pre-formed molecules selected from the group consisting of proteins, nucleic acids, polysaccharides and porphryins." Claims 8, 37 and 44 are dependent claims and are distinguished from Heller's list of most known biological molecules in column 6 lines 24-41 because Heller uses electrophoresis and not the pH shift from electrochemically-generated reagents. Moreover, the Examiner's reference to column 17 lines 1-7 just refers to nucleic acids.

With regard to claims 9 and 23, no concept of a linker molecule is presented in Heller column 21 lines 10-16. All that is present is the "buzzword" monomer used in a completely different context.

With regard to claims 11 and 24, the claims have been cancelled.

With regard to claims 12 and 27, the passage from Heller cited by the Examiner i(column 20, lines 25-35) teaches away from the invention of claims 12 and 27. The present invention (claims 12 and 27) provides an acid or base labile protecting group. When used in the context of claim 1, for example, this invention removes the protecting group in response to a pH change from an electrochemically-generated reagent (such as a proton or hydroxyl ion). In contrast, the passage cited in Heller refers to a "device to *transport*, *concentrate* and *react*" as the active verbs. It should be noted that Heller does not teach or suggest controlling pH changes in regions as provided in the invention of claims 12 and 27. Therefore, Heller again does not teach or even remotely suggest that which the Examiner alleges.

With regard to claims 13, 14, 29-31 and 40, these claims depend from independent claims 1 and 16. . What Heller does not teach or suggest is the respective subject matter found in each independent claim of the foregoing dependent claims. Applicant reasserts the above arguments regarding the patentability of claims 1 and 16 over Heller in view of Southern with respect to dependent claims 13, 14, 29-31 and 40.

With regard to the rejections of claim 15, 17, 42 and 47, Applicant traverses by respectfully disagreeing with the Examiner's characterization of Heller column 15 lines 48-58. That section refers to the "ability to electronically concentrate reactants or analytes on a specific micro-location." This section is not "sequentially deprotecting other protected chemical functional group of the monomer or pre-formed molecule." Applicant respectfully suggests that the Examiner may be confusing the claimed invention and what is described in Heller.

With regard to the rejection of claim 25, Applicant traverses by respectfully disagreeing with the Examiner's characterization of Heller. The passages from column 10 in Heller refer to the fabrication of the electrode array. The passage from column 17 refers to the use of "controlled porosity glass" as a support in a conventional DNA synthesizer. None of these sections teach "the use of glass as overlaying layers."

With regard to the rejection of claim 26, Applicant respectfully traverses by asserting that Heller fails to teach cleaving anything with "a group cleavable by an electrochemically generated reagent." That passage came from the claimed invention and not from Heller.

With regard to the rejection of claims 28, 32 and 33 the fact that independent claim 16, from which these claims depend, is patentable over Heller in view of Southern as described above, renders them similarly patentable.

With regard to the rejection of claim 34, Applicant respectfully disagress with the Examiner's position and suggests that the Examiner may have misunderstood the cited example from Heller.. Heller example 5 (cited by the Examiner) refers to metal oxide and metal-linked hydroxide groups (with aluminum) as electrode surface moieties for binding. This example teaches away from the invention of claim 34.

With regard to the rejection of claim 35, the process of capping an oligonucleotide is well known prior to Southern. The fact that claim 35 depends from claim 16 which, is patentable over Heller in view of Southern as described above, renders it similarly patentable.

With regard to the rejection of claims 36 and 38, Applicant respectfully disagrees with the Examiner's characterization of Heller as teaching deprotected functional groups. Unfortunately, the Examiner did not point to a section of Heller supporting this characterization of the reference.

Finally, with regard to the rejection of claim 39, Applicant respectfully disagree with the Examiner's characterization of Heller column 25, lines 1-3. This passage refers to fluorescent signaling from hybridization and is unrelated to the notion of CMOS circuitry to electronically address electrodes that is the subject matter of claim 39.

Improper Combination of References

In order to combine references, there must be some suggestion expressed within the references to suggest their combination. No such suggestion can be found in Heller that describes electrophoresis techniques nor in Southern that describes a limited and different (see above) electrochemical technique. The Examiner even acknowledges this fact in the "Response to Arguments" section on page 10-12 of the Office Action. However, Applicant has not "recognized an advantage" but Applicant has developed an entirely different process and microarray from either the Heller device (currently marketed by Nanogen Corporation) or the Southern experimental prototype that has never been commercialized. Applicant's current success in placing its microarray devices with key customers (such as Genentech and other major biotechnology companies) is evidence of commercial success and is a secondary consideration of patentability.

Response to Arguments

The arguments presented on pages 11 and 12 are based upon the improper characterizations of Heller noted throughout the discussion above. Electrophoretic processes do not remove protecting groups. Applicant's invention is much more than an improvement over Heller, it is an entirely different and unrelated technique that bears no relationship to Heller. Moreover, Heller does not teach the use of buffers to control regions of pH shifts because Heller

uses electrophoresis and teaches away from any generation of electrochemical reagents. Therefore, Southern cannot be combined with Heller.

Moreover, the combined teachings of Heller and Southern (if they could be properly combined) do not teach the claimed microarray device or methods for synthesis because the electrophoresis fields would cause movement of charged molecules and cause the system to completely fail. Therefore, the combined teachings of Heller and Southern would be dysfunctional. Hence the combination is an improper combination of two unrelated references.

Accordingly, in view of the foregoing remarks, applicant submits that the pending claims are patentable over Heller in view of Southern.

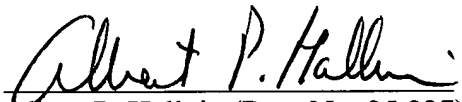
In view of the foregoing amendment and remarks, applicant respectfully requests withdrawal of the rejections, and allowance of pending claims 1-9, 12-23 and 25-51.

CONCLUSION

Applicants submit that the claims are now in condition for allowance and earnestly seek rapid advancement as such. Should any questions arise in connection with this submission which may be resolved by a telephonic interview, the Examiner is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

Date: April 24, 2001



Albert P. Halluin (Reg. No. 25,227)
Adam K. Whiting (Reg. No. 44,400)

HOWREY SIMON ARNOLD & WHITE, LLP
Box No. 34
301 Ravenswood Avenue
Menlo Park, CA 94025
(650) 463-8109